In the United States Court of Federal Claims

OFFICE OF SPECIAL MASTERS

Filed: December 18, 2015

DONNA RAMSAY,	*	PUBLISHED
Petitioner,	*	Case No. 11-549V
v.	*	Special Master Hamilton-Fieldman
SECRETARY OF HEALTH AND HUMAN SERVICES,	*	Causation; Gardasil Vaccine; Human Papillomavirus ("HPV") Vaccine; Juvenile Idiopathic Arthritis ("JIA").
Respondent.	*	

Patricia Leigh O'Dell, Beasley, Allen, et al., Montgomery, AL, for Petitioner.
Darryl Wishard, United States Department of Justice, Washington, DC, for Respondent

RULING ON ENTITLEMENT[1]

On August 30, 2011, Tina Ramsay filed a vaccine claim under the National Vaccine Injury Compensation Program ("the Program")[2] on behalf of her minor daughter, Donna Ramsay (hereinafter "Petitioner").[3] Ms. Ramsay alleged that as a result of receiving human papillomavirus ("HPV" or "Gardasil") vaccines on March 19, 2008 and June 30, 2008, Petitioner suffered from systemic Juvenile Idiopathic Arthritis ("sJIA").[4]

[1] Because this unpublished ruling contains a reasoned explanation for the undersigned's action in this case, the undersigned intends to post this order on the United States Court of Federal Claims website, in accordance with the E-Government Act of 2002, Pub. L. No. 107-347, § 205, 116 Stat. 2899, 2913 (codified as amended at 44 U.S.C. § 3501 note (2006)). As provided by Vaccine Rule 18(b), each party has 14 days within which to request redaction "of any information furnished by that party: (1) that is a trade secret or commercial or financial in substance and is privileged or confidential; or (2) that includes medical files or similar files, the disclosure of which would constitute a clearly unwarranted invasion of privacy." Vaccine Rule 18(b). Otherwise, "the entire" order will be available to the public. *Id.*

[2] The Program comprises Part 2 of the National Childhood Vaccine Injury Act of 1986, Pub. L. No. 99-660, 100 Stat. 3755, codified as amended, 42 U.S.C. §§ 300aa-10 *et seq.* (hereinafter "Vaccine Act" or "the Act"). Hereafter, individual section references will be to 42 U.S.C. § 300aa of the Act.

[3] Donna Ramsay, who has reached the age of majority since the petition was filed, has since been substituted as Petitioner. *See* Order, December 16, at 1.

[4] Throughout the record, Petitioner's sJIA has alternatively been referred to as juvenile rheumatoid arthritis ("JRA") and Still's disease. These three terms refer to the same injury. *See, e.g.*, Transcript ("Tr.") at 39-40.

The undersigned now finds that Petitioner has proven, by a preponderance of the evidence, that her sJIA was caused by her HPV vaccinations. The Clerk's Office is ordered to enter judgment in favor of Petitioner unless a motion for review is filed.

I. Facts

Petitioner was born on June 16, 1993. Petitioner's Exhibit ("Pet. Ex.") 1 at 1. Prior to administration of the first and second Gardasil vaccinations, Petitioner's medical history was unremarkable except for a tonsillectomy at age seven and migraine headaches and irritable bowel syndrome diagnosed at age twelve. Pet Ex. 3 at 11; Pet. Ex. 4 at 47-48. Petitioner asserts, and the records do not contradict, that she had no adverse reactions to any vaccination prior to administration of the Gardasil vaccine. *See* Petitioner's Post-Hearing Brief at 1.

Petitioner was administered the first Gardasil vaccine on March 19, 2008, when she was fourteen years old. Pet. Ex. 2 at 3-4. She was administered the second Gardasil vaccine on June 30, 2008, when she was fifteen years old. Pet. Ex. 3 at 11; Pet. Ex. 13 at 1.

The medical records are inconclusive regarding the precise date of onset of Petitioner's sJIA. According to an affidavit authored by Tina Ramsay, Petitioner "began having flu-like symptoms, such as sore throat, fever and aching all over her body" during the first week of November 2008. Pet. Ex. 9 at 1; *see also* Pet. Ex. 6 at 46 (reporting that "aches and pains" began "in the first part of November," followed by headache, red eyes, and fever). Petitioner did not seek medical attention, however, until November 13, 2008, when she presented to her primary care physician, Dr. Carl Brutkiewicz, with complaints of muscle aches, fever, and wrist pain, as well as "irritated eyes and headaches over the last week." Pet. Ex. 3 at 12; Pet Ex. 5 at 42. Her temperature was 99.1 degrees. Pet. Ex. 3 at 12. Dr. Brutkiewicz diagnosed Petitioner with allergies and prescribed Petitioner with Xyxal #10 (anti-allergy eyedrops). *Id*. Dr. Brutkiewicz would later describe her exam at this visit as "fairly unremarkable." Pet. Ex. 5 at 38.

On November 14, 2008, Petitioner's mother, Tina Ramsay, called in to Dr. Brutkiewicz's office and reported that Petitioner was "achy all over today," with a fever of 100.6 and headaches. Pet. Ex. 3 at 12. She was prescribed amoxicillin. *Id*. No rash was reported, either during this call or during the November 13, 2008 exam.

On November 16, 2008, Petitioner reported to Mobile Infirmary West with generalized rash and myalgia.[5] Pet. Ex. 4 at 29; *see also* Pet. Ex. 5 at 42 (noting retrospectively that Petitioner's rash developed in mid-November). She was referred to the University of South Alabama Children's and Women's Hospital (hereinafter "South Alabama Hospital"), where she reported that she had been experiencing "all over" aches and pain "off and on" for about a week. Pet. Ex. 4 at 44. An exam revealed "pink, raised macular papular rashes on both arms" which "blanch [] on pressure." *Id*. at 49. Tests for various infectious etiologies and systemic autoimmune diseases were all negative. See Pet. Ex. 4 at 29, 49 (documenting that monospot, C-

[5] Myalgia is muscle pain. *Dorland's Illustrated Medical Dictionary* ("*Dorland's*"), 1214 (32d ed. 2012).

reactive protein ("CRP"),[6] antistreptolysin O ("ASO") titer, an ESR, and a rapid strep test were all negative; *see also* Petitioner's Post-Hearing Brief at 2. Petitioner was administered IV fluids and IV penicillin before being discharged on November 17, 2008, with a diagnosis of "viral illness." Pet. Ex. 4 at 29.

On November 20, 2008, Petitioner presented to the emergency department of South Alabama Hospital "[with complaints of] fever, myalgia for 8 days." Pet. Ex. 4 at 14. According to Petitioner's mother, Petitioner's fevers, rash, and myalgias had persisted after she was prescribed amoxicillin; her maximum temperature had been 104. *Id*. Upon exam, "patchy erythematous rash"[7] was noted. *Id*. Petitioner was diagnosed with mononucleosis,[8] prescribed Tylenol and naproxen,[9] and discharged. *Id*. at 4, 17.

She followed up with Dr. Brutkiewicz on November 21, 2008. Pet. Ex. 3 at 12. Petitioner reported that her "diffuse aches" had continued despite medication. *Id*. Dr. Brutkiewicz noted that Petitioner had a temperature of 100.8, "moderate pharyngeal erythema," diffuse myalgias, and a fading macular rash on her upper extremities. *Id*. He diagnosed her with "probable viral syndrome with post viral _____." *Id*.

On November 24, 2008, Petitioner was admitted to Springhill Memorial Hospital (hereinafter "Springhill") for treatment of a "fibrile [sic] illness." Pet. Ex. 5 at 37. Upon admission, her temperature was documented at 103.2. Pet. Ex. 5 at 38. Her condition had "progressed to generalized aches and pains of all of her joints and extremities." *Id*. at 42. "[I]ntermittent macular rash on … her extremities and hands" was noted. *Id*. at 37, 42. Testing revealed that Petitioner's white blood cell count was elevated to 22,500; monospot, throat culture, DNAase B titer, ASO titer, Hepatitis B surface antigen, Hepatitis C antibody, Parvovirus B19 IgG/ IgM, ANA profile, rheumatoid factor, and Mycoplasma[10] IgM tests, as well as a PPD

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[6] C-reactive protein is "a globulin that forms a precipitate with the somatic C-polysaccharide of the pneumococcus in vitro; it is the most predominant of the acute phase proteins." Dorland's at 1532. CRP "is found in the serum of various people with certain inflammatory, degenerative, and neoplastic diseases." *Stedman's Medical Dictionary* ("*Stedman's*"), 1580 (28th ed. 2006).

[7] Erythema is defined as a "redness of the skin produced by congestion of the capillaries." *Dorland's* at 643.

[8] A monospot test performed three days prior to this diagnosis, at the same hospital, had been negative. Pet. Ex. 4 at 29.

[9] Naproxen is "a nonsteroidal antiinflammatory drug that is a propionic acid derivative, used in the treatment of pain, inflammation, osteoarthritis [and] rheumatoid arthritis," among other conditions. *Dorland's* at 1232.

[10] Mycoplasma is "a genus of bacteria of the family Mycoplasmataceae, made up of round, highly pleomorphic, gram-negative cells that are bounded by a single triple-layered membrane and lack a true cell wall." Mycoplasma pneumo'niae is "a species that often causes inapparent infections or mild respiratory tract disease but can also cause mycoplasmal pneumonia." *Dorland's* at 1216-1217.

test for tuberculosis, were all negative. *Id*. at 21-22, 45, 160-67. Petitioner's CPK[11] was noted to have been low (at 190), and her ferritin and adolase were elevated (at 4413 and at 12.5, respectively). *Id*. at 21-22, 160-67. Her sedimentation rate[12] was 105. *Id*. While hospitalized, Petitioner was administered steroids, which "significantly" improved her condition by decreasing her joint pain, resolving her fever, and reducing her rash. *Id*. at 41. Petitioner was discharged on November 28, 2008, with diagnoses of "probable autoimmune disease," febrile illness, arthralgias,[13] elevated sedimentation rate, elevated CRP, elevated ferritin level, and polymorphous rash. *Id*. at 45.

Several of Petitioner's treatment providers at Springhill noted that her condition was consistent with sJIA. Dr. Teresa Oglesby, a consulting rheumatologist, opined that, clinically speaking, her illness was consistent with a "postviral" event or with Still's disease. *Id*. at 29. Among other things, Dr. Oglesby observed that an elevated ferritin level was commonly associated with Still's. *Id*. at 25. Dr. Adrien Bodet, an infectious disease specialist, suspected either "1) [p]ost-infectious inflammatory [disease] or 2) [primary] immune [reaction] (Still's?)." *Id*. at 24. *See also* Pet. Ex. 5 at 41 (Dr. Sindel stated that "Still's disease [is still] a consideration").

After her discharge from Springhill, Petitioner followed up with Dr. Daren Scroggie, a pediatric rheumatologist. Pet. Ex. 6 at 45-47. Following a visit on December 1, 2008, Dr. Scroggie concluded that Petitioner "has a history consistent with systemic onset JIA, though she is still early on." *Id*. at 47; *see also* Pet. Ex. 3 at 10 (Dr. Brutkiewicz noting Dr. Scroggie's presumptive diagnosis of Still's disease on December 4, 2008). On December 8, 2008, Dr. Scroggie prescribed methotrexate.[14] Pet. Ex. 6 at 44. As of December 22, 2008, Dr. Scroggie observed that Petitioner "[was] doing better and approaching baseline from [a] joint standpoint." Pet. Ex. 6 at 41.

Throughout 2009, Petitioner's physicians continued to treat her illness with methotrexate and steroids. *See, e.g.*, Pet. Ex. 6 at 3, 44. In 2010, Petitioner's treaters also began referring to a diagnosis of Crohn's-related arthritis. *See, e.g.*, Pet. Ex. 8 at 81. As Respondent concedes, "[these physician] notes lack sufficient clarity to establish the basis for a change from JIA to Crohn's as the diagnosis." Respondent's Rule 4 Report at 5; *see also* tr. 43-44 (Respondent declining to contest the accuracy of Petitioner's sJIA diagnosis).

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[11] CPK refers to creatine phosphokinase and creatine kinase, an "enzyme of the transferase class that catalyzes the phosphorylation of creatine by ATP to form phosphocreatine." *Dorland's* at 427, 429.

[12] The erythrocyte sedimentation rate (ESR) [hereinafter "sedimentation rate"] is "the rate at which erythrocytes precipitate out from a well-mixed specimen of venous blood … an increase in rate is usually due to elevated levels of plasma proteins, especially fibrinogen and immunoglobulins." *Dorland's* at 1594. It is increased in "active inflammatory disease," among other things. *Id*.

[13] Arthralgia is joint pain. *Dorland's* at 150.

[14] Methotrexate is "a folic acid antagonist that acts by inhibiting synthesis of DNA, RNA, thymidylate, and protein …. It is [] used as an antipsoriatic and antiarthritic in the treatment of severe, recalcitrant, disabling psoriasis and severe rheumatoid and psoriatic athritis." *Dorland's* at 1151.

II. Procedural Overview

Tina Ramsay filed this vaccine petition on Petitioner's behalf on August 30, 2011. The case was initially assigned to Special Master Gary Golkiewicz. Medical records, including Exhibits 1 through 13, as well as a statement of completion, were filed between October 25, 2011 and December 28, 2011. On December 28, 2011, Petitioner filed an expert report authored by Dr. Michael McCabe. *See* Pet. Ex. 14. The references cited in Dr. McCabe's report were filed on January 6, 2012. *See* Pet. Ex. 15-36.

On March 20, 2012, Respondent filed a Rule 4 Report recommending against compensation because, Respondent argued, Petitioner had not established by a preponderance of the evidence that Petitioner had suffered a vaccine-related injury. Rule 4 Report ("Resp. Report") at 1, 6-14. Simultaneously, Respondent filed an expert report authored by Dr. Carlos Rose. *See* Respondent's Exhibit ("Resp. Ex.") A.

At a status conference held on March 29, 2012, Special Master Golkiewicz and "[t]he parties discussed how to address respondent's concerns regarding the proper medical diagnosis and whether Dr. McCabe … is qualified to address such an issue." *See* Order, filed March 30, 2012, at 1. Special Master Golkiewicz noted that "petitioner's expert's reasoning regarding a medically appropriate time frame between vaccination and onset of injury is problematic." *Id*.

On April 30, 2012, Petitioner filed a status report in which she stated that her treating rheumatologist, Dr. Peter Weiser, had agreed to write a letter clarifying Petitioner's diagnosis. Petitioner requested the opportunity to file Dr. Weiser's letter, as well as a supplemental expert report authored by Dr. McCabe. Both of these requests were granted. *See* Order, filed May 1, 2012, at 1.

On May 9, 2012, this case was reassigned to then-Chief Special Master Campbell-Smith.

Petitioner ultimately filed Dr. Weiser's letter on May 22, 2012; she filed Dr. McCabe's supplemental expert report on June 15, 2012.[15] *See* respectively Pet. Exs. 37, 38.

On July 11, 2012, Chief Special Master Campbell-Smith convened a status conference during which she advised Petitioner to clarify the nature of Petitioner's injury, to "address the medical appropriateness of the four-month period between the onset of [Petitioner's] symptoms and her receipt of the vaccinations at issue," and "to address the impact, if any, of a clarified diagnosis of either sJIA or Crohn's disease" on Dr. McCabe's theory of causation. *See* Order, July 12, 2012, at 2-3. Among other things, Chief Special Master Campbell-Smith observed that the factual predicate underlying Petitioner's theory remained unclear. *Id*. at 2. She directed Petitioner to file clarifying opinions from Petitioner's treating gastroenterologist, Dr. Jeanine Maclin, "regarding the basis for the diagnostic impression that [Petitioner] has Crohn's disease;" from Dr. Weiser "clarify[ing] whether he attributes [Petitioner's] inflammatory condition to a

[15] In the interim, Chief Special Master Campbell-Smith granted a motion for extension of time to file Dr. Weiser's letter. *See* Non-PDF Order, filed May 16, 2012.

diagnosis of sJIA or Crohn's disease;" and from Dr. McCabe regarding the timeliness of onset. *Id*. at 3. Petitioner ultimately filed clarifying opinions from Dr. Maclin and Dr. McCabe on October 9, 2012. *See* Pet. Exs. 39 (Dr. Maclin) and 40 (Dr. McCabe). Petitioner declined to file an additional report from Dr. Weiser.[16] *See* Status Report, filed October 15, 2012, at 1.

During a status conference held on November 21, 2012, Chief Special Master Campbell-Smith began the process of scheduling an entitlement hearing. *See* Order, filed November 21, 2012, at 1-2. A pre-hearing order was issued on December 6, 2012. Petitioner filed three additional medical literature exhibits on November 30, 2012, *see* Pet. Exs. 41-43, and Respondent filed a final expert report authored by Dr. Rose, as well as supportive medical literature, on January 7, 2013. *See* Resp. Exs. G-J.

On March 4, 2013, this case was reassigned to the undersigned.

On June 7, 2013, Petitioner moved to continue the entitlement hearing that had been set for August 5, 2013 and August 6, 2013, as well as its associated pre-trial deadlines. Motion to Continue Entitlement Hearing and Pre-Trial Deadlines, filed June 7, 2013, at 1-2. Petitioner's counsel requested that the hearing be postponed pending appellate review of a decision denying entitlement in a similar case. *See Koehn v. Sec'y of Health & Human Servs.*, 773 F.3d 1239 (Fed. Cir. 2014) (affirming denial of entitlement in a Gardasil/ sJIA case that had been filed by Ms. O'Dell on the basis of Dr. McCabe's theory of causation). *Id*. Respondent objected to the requested continuance. *Id*. at 2. The undersigned ultimately denied Petitioner's motion to continue, noting that there are "distinctive factual and medical differences between this case and the *Koehn* case," and that *Koehn*'s outcome was not binding on the undersigned. *See* Order, June 11, 2013, at 2.

On June 20, 2013, the undersigned granted Petitioner's motion to file a supplemental expert report, this time authored by Dr. Eric Gershwin. *See* Order, filed June 20, 2013; Motion, filed June 18, 2013. Petitioner filed Dr. Gershwin's expert report, as well as supportive medical literature, on June 26, 2013. *See* Pet. Exs. 44-65. Petitioner filed additional medical literature, as well as her experts' CVs, on July 12, 2013. *See* Pet. Exs. 66-83.

An entitlement hearing was held in Washington, D.C., on August 5th and 6th, 2013. Both parties' experts testified. At the close of the hearing, the undersigned granted Petitioner's counsel's request to file post-hearing briefs. Tr. 428-31. The parties simultaneously filed post-hearing briefs on September 3, 2013. This matter is now ripe for a ruling.

III. Analysis

A. Standards of Adjudication

To receive compensation under the Vaccine Act, Petitioner must demonstrate either that: (1) she suffered a "Table injury" by receiving a covered vaccine and subsequently developing a

[16] Chief Special Master Campbell-Smith granted Petitioner two extensions to file these reports. *See* Non-PDF Orders of August 10, 2012; September 7, 2012.

listed injury within the time frame prescribed by the Vaccine Injury Table set forth at 42 U.S.C. § 300aa-14, as amended by 42 C.F.R. § 100.3; or (2) that suffered an "off-Table Injury," one not listed on the Table as a result of her receipt of a covered vaccine. *See* 42 U.S.C. §§ 300aa-11(c)(1)(C); *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321 (Fed. Cir. 2010); *Capizzano v. Sec'y of Health & Human Servs.*, 440 F.3d 1317, 1320 (Fed. Cir. 2006).

Because Petitioner does not allege a Table injury in this case, she must prove that her injury was caused-in-fact by an covered vaccine. To establish causation-in-fact, Petitioner must demonstrate by a preponderance of the evidence that the vaccine was the cause of the injury. 42 U.S.C. § 300aa-13(a)(1)(A). Petitioners are required to prove that the vaccine was "not only [the] but-for cause of the injury but also a substantial factor in bringing about the injury." *Moberly v. Sec'y of Health & Human Servs.*, 592 F.3d 1315, 1321-22 (Fed. Cir. 2010) (quoting *Shyface v. Sec'y of Health & Human Servs.*, 165 F.3d 1344, 1352-53 (Fed. Cir. 1999)).

In the seminal case of *Althen v. Secretary of the Department of Health and Human Services*, the Federal Circuit set forth a three-pronged test used to determine whether a petitioner has established a causal link between a vaccine and the claimed injury. *See Althen v. Sec'y of Health & Human Servs.*, 418 F.3d 1274, 1278-79 (Fed. Cir. 2005). The *Althen* test requires the petitioners to set forth: "(1) a medical theory causally connecting the vaccination and the injury; (2) a logical sequence of cause and effect showing that the vaccination was the reason for the injury; and (3) a showing of a proximate temporal relationship between vaccination and injury." *Id.* To establish entitlement to compensation under the Program, a petitioner is required to establish each of the three prongs of *Althen* by a preponderance of the evidence. *See id.*

Specifically, under the first prong of *Althen*, Petitioners must offer a scientific or medical theory that answers in the affirmative the question "can the vaccine(s) at issue cause the type of injury alleged?" *See Pafford v. Sec'y of Health & Human Servs.*, No. 01-0165V, 2004 WL 1717359, at *4 (Fed. Cl. Spec. Mstr. July 16, 2004). This may be accomplished in a number of ways. *Id.* "Reliability and plausibility of pathogenesis can be bolstered by providing evidence that at least a sufficient minority in the medical community has accepted the theory, so as to render it credible." *Id.* In addition, "epidemiological studies and an expert's experience, while not dispositive, lend significant credence to the claim of reliability; articles published in respected medical journals, which have been subjected to peer review, are also persuasive." *Id.* However, publication "does not necessarily correlate with reliability," because "in some instances well-grounded but innovative theories will not have been published." *Daubert v. Merrell Dow Pharmaceuticals, Inc.*, 509 U.S. 579, 593–94 (1993).

In addition to showing that the vaccine at issue can cause a particular injury, a petitioner must also prove that the vaccine actually *did* cause the alleged injury in a particular case. *See Pafford*, 2004 WL 1717359, at *4 (emphasis added); *Althen*, 418 F.3d at 1279. A petitioner does not meet this obligation by showing a temporal association between the vaccination and the injury; the petitioner must explain "how and why the injury occurred." *Pafford*, 2004 WL 1717359, at *4.

While a temporal association alone is insufficient to establish causation under the third prong of *Althen*, a petitioner must show that the timing of the injury fits with the causal theory.

See Althen, 418 F.3d at 1278. For example, if the petitioner's theory involves a process that takes several days to develop after vaccination, an injury that occurred within a day of vaccination would not be temporally consistent with that theory. Conversely, if the theory is one that anticipates a rapid development of the reaction post-vaccination, the development of the alleged injury weeks or months post-vaccination would not be consistent with that theory. The special master cannot infer causation from temporal proximity alone. In fact, it has been held, that where a petitioner's expert views the temporal relationship as the "key" indicator of causation, the claim must fail. *See Thibaudeau v. Sec'y of Health & Human Servs.*, 24 Cl. Ct. 400, 403-04 (Fed. Cl. Oct. 23, 1991); *see also Grant v. Sec'y of Health & Human Servs.*, 956 F.2d 1144, 1148 (Fed. Cir. 1992); *Hasler v. United States*, 718 F.2d 202, 205 (6th Cir. 1983) (stating that inoculation is not the cause of every event that occurs within a ten-day period following it).

A petitioner who demonstrates by a preponderance of the evidence that he suffered an injury caused by vaccination is entitled to compensation, unless the respondent can demonstrate by a preponderance of the evidence that the injury was caused by factors unrelated to the vaccination. *See Althen*, 418 F.3d at 1278; *Knudsen v. Sec'y of Health & Human Servs.*, 35 F.3d 543, 547 (Fed. Cir. 1994).

B. The Parties' Arguments

i. Petitioners' Arguments

1. Dr. Eric Gershwin

a. Qualifications

Dr. Eric Gershwin received his medical degree from Stanford University in 1971. Pet. Ex. 67 at 1; tr. 5. He has been board-certified in internal medicine, rheumatology, and allergy and clinical immunology since 1974, 1978, and 1980, respectively. Pet. Ex. 67 at 2; tr. 7. He is currently a professor of medicine at the University of California School of Medicine in Davis, California; since 1982, he served as the school's chief of the Division of Rheumatology/ Allergy and Clinical Immunology. Pet. Ex. 67 at 1; tr. 6-7.

Between 1960 and the date of the entitlement hearing, Dr. Gershwin had published 859 peer-reviewed articles. Pet. Ex. 67 at 13-82; tr. 10. He has also written numerous books, book chapters, and reviews. Tr. 7-10. Of particular note are Dr. Gershwin's role in editing the first published book on musculoskeletal diseases in children, and in publishing a peer-reviewed article on issues related to the roles of familial factors, environmental factors, and activating macrophages in juvenile arthritis. *See generally* Pet Ex. 67. Dr. Gershwin has published articles specifically on the role of pro-inflammatory cytokines in sJIA. *See, e.g.*, Pet. Ex. 46.

At hearing, Dr. Gershwin was admitted as an expert in rheumatology and immunology. Tr. 11.

b. Theory

Dr. Gershwin declined to opine in favor of causation in this case, citing a lack of supportive epidemiological evidence. *See generally* Pet. Ex. 44; tr. 17, 30-31 (agreeing that "a vaccine [can] be a trigger in a genetically susceptible host" and that vaccines are a "risk factor" for Still's, but that he "would not write a vaccination produced a disease, like Still's disease, at all …. [There is] no evidence that it [can] produce [] a disease like Still's [in the absence of] a clear-cut epidemiologic analysis, which, of course, with an incidence of … less than one per hundred thousand, it's just not possible in Still's").

He agreed, however, that sJIA "is a disease caused by a genetic predisposition," that it needs "some environmental stimulus to set it off," and that a vaccine can constitute this environmental stimulus "in some people." Tr. 17, 40-41. According to an article of which Dr. Gershwin was a co-author, sJIA is "defined by arthritis with spiking fever persisting for more than 2 weeks and at least one of the clinical features of systemic inflammation: skin rash, lymphadenopathy,[17] hepatosplenomegaly,[18] or serositis[19] (pleuritis or pericarditis)." Pet. Ex. 46[20] at 2. sJIA is "very rare;" the incidence is less than one case per 100,000 per year. Tr. 12. The rarity of its incidence is attributable to the fact that it is a polygenic[21] ailment; its occurrence depends on a rare combination of variants, as well as a trigger. Tr. 296.

sJIA is an autoinflammatory disease:[22] it is characterized by abnormality in the functioning of the innate immune system. Tr. 15-17, 25-27 ("there are no obvious auto-antibodies … but they seem to have an exaggerated innate response, and so they're called autoinflammatory."), 40. The innate system consists of first responders, in contrast to the adaptive immune system, which consists of secondary responders. Tr. 14, 16. Dr. Gershwin explained that, notwithstanding sJIA's identity as an autoinflammatory disease, the adaptive immune system plays a role in its development. Tr. 15. The innate and adaptive immune systems "interact with each other [like] … two wheels with cogs;" "the only way that both wheels will function is if the cogs turn at the same time or in … some residence with each other."

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[17] Lymphadenopathy is "disease of the lymph nodes, usually with swelling." *Dorland's* at 1083.

[18] Hepatosplenomegaly is "enlargement of the liver and spleen." *Dorland's* at 847.

[19] Pleuritis is inflammation of the lung membrane; pericarditis is inflammation of the tissue of the heart. *Dorland's* at 1460-61, 1411-12.

[20] Lin, Y., et al., *The pathogenesis of oligoarticular/ polyarticular vs. systemic juvenile idiopathic arthritis*, Autoimmun. Rev., 2011; 10: 482-489 [hereinafter "*Lin*"].

[21] Polygenic is "pertaining to or determined by the action of multiple different genes." *Dorland's* at 1489.

[22] Autoinflammatory is defined as "characterized by a disorder of the body's innate immunity, with inflammation that is not caused by an external irritant such as infection." *Dorland's* at 181. Autoimmune disease, in contrast, is "characterized by a specific humoral or cell-mediated immune response against constituents of the body's own tissue constituents." *Id*.

Id. at 14. Adaptive immunity only responds if it senses a threat, like infection; in cases of autoimmune disease, the adaptive immune system attacks itself. Tr. 15.

The uncontrolled activation – or "dysregulation" – of the innate immune response in sJIA patients results in continuous production – or "upregulation" – of certain types of proteins secreted by cells of the immune system. Tr. 15-16, 25-27, 35. These proteins are called proinflammatory cytokines. *Id*. at 16. Specific cytokines - including interleukin-1 ("IL-1), interleukin-6 ("IL-6"), and interleukin-18 ("IL-18"), among others – are associated with sJIA. Tr. 15-16.[23] Cytokines are difficult to measure by any objective test;[24] though they can be assessed indirectly with reference to clinical markers, these markers will not be apparent until a cytokine "breakthrough" or "storm" occurs. Tr. 26-28, 35-36. Once the clinical threshold is met, symptoms may include fever, achy joints, inflammation, and swelling in parts of the body, including the pleura.[25] Tr. 12-13, 35-36. After upregulation of these cytokines has begun, they continue to amplify and recruit other cells. Tr. 25-27.

The Gardasil vaccine, by design, stimulates both the innate and adaptive immune systems. Tr. 14. Like other vaccines, it is capable of precipitating autoimmune diseases. Tr. 30-31. Moreover, Dr. Gershwin testified that sJIA is a genetic disease and that it can be prompted by an environmental trigger. Tr. 16-17. According to Dr. Gershwin, studies have shown that the concordance of sJIA among identical twins is "quite low," "which means that although genetics are important, environment has to start it off. *Id.* at 17. There has to be something that takes a genetically predisposed person to produce inflammation." Tr. 17.

With respect to the instant case, Dr. Gershwin observed that Petitioner presented to her treatment providers in November 2008 with symptoms that included fever, headache, and sore throat; a high white blood cell count; and elevated C-reactive protein, all of which are consistent with a Still's presentation. Tr. 36-38. Dr. Gershwin agreed that the onset of her sJIA was in November 2008, and that Petitioner exhibited no signs and symptoms of the disease between March and November 2008. Tr. 44. Dr. Gershwin also observed that Petitioner's treatment regimen provides additional evidence that her injury was caused by upregulation of the cytokines associated with sJIA: Petitioner was successfully treated with steroids and methotrexate, both of which are drugs that inhibit the cytokines TNF-alpha, IL-6, and IL-1. Tr. 37-39; *see also* Pet. Ex. 6 at 34-36, 41.

Most importantly, Dr. Gershwin opined that four and a half months – the amount of time it took Petitioner's sJIA to manifest after the second Gardasil vaccine – is an appropriate interval

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[23] Cytokines are "a generic term for nonantibody proteins released by one cell population … on contact with specific antigen, which act as intercellular mediators, as in the generation of an immune response." *Dorland's* at 466.

[24] Dr. Gershwin testified that "[i]n some diseases, like rheumatoid arthritis, you can actually find evidence in the blood for years before they ever get sick. Not so in Still's. It hasn't even been looked at." Tr. 30.

[25] IL-6 concentrations, in particular, have been shown to rise and fall in concert with temperature spikes and drops (though IL-6 may be elevated even in the absence of a spiking fever). Tr. 48-50.

between a triggering event and sJIA manifestation. Tr. 16-30. Dr. Gershwin testified that "[t]he protective response … to the HPV vaccination takes about seven months [from the first shot]." Tr. 18-19, 30 ("the precipitation of [sJIA] ends up being an immunological imbalance, which takes time to develop …. Because the latency time is a significant period of time, and something is happening during that time."). In support of this testimony, Dr. Gershwin pointed to the results of the Frazer study, which showed that, among subjects who had received three HPV vaccinations, peak immune response occurred at approximately seven months after the first vaccination. Tr. 19-20; Pet. Ex. 29.[26] Conceding that *Frazer* did not study immune responses in individuals who had only received the first and second vaccines, Dr. Gershwin argued that the absence of a third vaccine was unlikely to have significantly altered the timing of her immune response. Tr. 20-27. Whether or not a third "booster" vaccination is administered, the first two Gardasil vaccinations are, by design, likely to prompt a significant immune response. Tr. 22.

According to Dr. Gershwin, Still's was likely to have eventually been triggered in someone with Petitioner's genetic predisposition. Tr. 41-42. There are multiple etiologies for the disease. Tr. 41. It is unlikely, however, that Petitioner's pre-existing IBS was the trigger, because IBS does not produce inflammation or cytokines. Tr. 42-43.

Dr. Gershwin acknowledged that, according to an article he co-authored in 2011 and that discussed "triggering factors" of sJIA, there has only been one case of "an exacerbation of systemic JIA" following vaccination. *Lin* at 5. In that case, onset occurred five days post-vaccination, and the vaccine at issue was live-attenuated rubella. *Id*. The individual studied had pre-existing Still's. *Id*.; tr. 45-47. The authors of the article contemplated molecular mimicry, rather than cytokines, as the initial mechanism of injury. *Lin* at 3 ("Vaccines, similar to infectious agents, may trigger autoimmune diseases through various mechanisms such as molecular mimicry of vaccine with self-antigens, antigen non-specific bystander activation and polyclonal lymphocyte activation during immune response to vaccine."). At hearing, Dr. Gershwin clarified that, even though the authors argued that the process was initiated by molecular mimicry, "the process of the inflammation, whether it's mimicry or not, it's still cytokines, absolutely, carved in concrete, inescapable in Still's." Tr. 52-54.

2. Dr. McCabe

a. Qualifications

Dr. Michael McCabe earned a Ph.D. in Microbiology and Immunology from Albany Medical College in 1991. Pet. Ex. 66 at 2. He subsequently served as a postdoctoral research associate at the Karolinska Institute in Sweden, where he studied cell-signaling and regulation of the cell death process. *Id*., tr. 58-59. Between 1992 and 2000, he was an assistant professor of chemical toxicology and pharmaceutical sciences at Wayne State University. Pet. Ex. 66 at 2. Between 2000 and 2009, Dr. McCabe served as an associate professor in the University of Rochester School of Medicine's Department of Environmental Medicine. *Id*. at 1. Between 2009 and the date of the hearing, Dr. McCabe served as an "associate" at Robson Forensic, Inc., "an expert witness consulting firm providing litigation support, expertise, [and] opinions [] to the

[26] Frazer, I., *Correlating immunity with protection for HPV infection*, Int. Society Infect. Dis., 2007; 11(S2): S10-S16 [hereinafter "*Frazer*"].

legal and insurance industries." *Id.*; tr. at 68. He has authored approximately 40 peer-reviewed articles and twelve book chapters, and is an editor of the Journal of Immunotoxicology. Pet. Ex. 66 at 4; 8-13.

At hearing, Dr. McCabe was admitted as an expert in immunology. Tr. 74.

b. Theory

1) The Gardasil vaccine is designed to elicit proinflammatory cytokines

Dr. McCabe's theories regarding the immune system's response to the Gardasil vaccine – and its role in the etiology of sJIA – are essentially consistent with those of Dr. Gershwin. Unlike Dr. Gershwin, however, Dr. McCabe believes that there is sufficient evidence upon which to conclude that Petitioner's Gardasil vaccinations caused her sJIA.

According to Dr. McCabe, Gardasil, which is designed to stimulate both the innate and adaptive immune systems, produces "a dramatic, robust, sustained response." Tr. 79-80, 128, 181. One aspect of this response is an upregulation of cytokines, which "participate both in adaptive immune signaling, as well as innate immune signaling, as well as interactions between the adaptive and innate immune system." Tr. 128. In particular, the vaccine causes a marked upregulation of the proinflammatory cytokines IL 6, TNF-alpha, and IL 1. Tr. 128-30. In practice, "Gardasil elicits proinflammatory cytokines in nearly everyone [to whom] the vaccine is administered," and "[i]n some genetically susceptible individuals, that trigger, cytokine upregulation, is an environmental trigger contributing to the causation of the disease [sJIA]." Tr. 80; Pet Ex. 14 at 4 ("the cause of sJIA is thought to be multifactorial – with genetic susceptibility factors and environmental triggers working together in complex ways to initiate and perpetuate adaptive and/or innate immune activities resulting in tissue damage.").

In support of his theory, Dr. McCabe relied heavily on a study of the cytokine responses elicited by the HPV-16 IL-1 viruslike particle (one of the components of the Gardasil vaccine)[27]. Pet. Ex. 30;[28] *see also* tr. 80-82. The Pinto study measured cytokine production in response to the particle at zero- (before the first dose), two- (a month after the second dose), and seven- (one month after the third dose) month intervals. Pet. Ex. 30 at 4; tr. 83-84, 94. The Pinto data show that, "under both time frames, the two -month [after the first dose] and the seven-month [after the third dose],… you get appreciable production of IL-6 at both time points." Tr. 91. Within the time frame of the experiment, IL-6 cytokine production increased 50-fold. Tr. 100-01. The proinflammatory cytokines THF-alpha and IL-1 beta were similarly elicited over time, "the time being tied to the immunization protocol schedule that these individuals received," though to a

[27] Dr. McCabe testified that the absence of an adjuvant does not limit the application of the Pinto data to "what we expect with the quadrivalent [Gardasil] vaccine." Tr. 81-82.

[28] Pinto, L., et al., *HPV-16 L1 VLP vaccine elicits a broad-spectrum of cytokine responses in whole blood*, Vaccine, 2005; 23: 3555-64 [hereinafter "the Pinto study" or "*Pinto*"].

lesser extent. Pet. Ex. 30 at 4; tr. 97, 101 (noting that there was a four-fold increase in TNF-alpha and a nine- or ten-fold increase in IL-1).

According to Dr. McCabe, the Pinto study data have largely been confirmed by other medical literature. A 2007 study, the results of which were reported by lead author Garcia-Pineras, revealed a seven-fold increase in IL-6 production following three doses of Gardasil. Pet. Ex. 31 at 2;[29] tr. 102-03. The Garcia-Pineras study did not reveal dramatic changes in TNF or IL-1. Pet. Ex. 31 at 2; tr. 102-03. Participants in the Garcia-Pineras study did not receive an adjuvant, which would likely have increased the response; responses were measured pre-vaccination and post-vaccination, but not between doses. Tr. 170-71.

Dr. McCabe also cited the Evans study, which examined individuals at zero-, four-, and 16-week intervals and showed "a dramatic increase" in IF-gamma and IL-5 as a function of vaccination, Pet. Ex. 33[30] at 2-4; tr. 110-11. A study by Emeny, in which the immunization schedule was at zero, two, and six months, documented upregulation of IF-gamma, IL-5, and IL-2 cytokines. Pet. Ex. 35[31] at 7; tr. at 111.

Dr. McCabe conceded that none of the articles he cites studied arthritis or sJIA specifically; they assessed only the cytokine responses in their subjects. Tr. 169-71. Dr. McCabe also conceded that there are no published case reports, case control studies, or animal models that show a relationship between HPV vaccines and sJIA. Tr. 154. Moreover, neither the Meningococcus C nor the Measles-Mumps-Rubella ("MMR") vaccinations, both of which had been suggested as triggers and which were subject to prospective and retrospective studies, have been confirmed to trigger sJIA. Pet. Ex. 16,[32] tr. 158-59. Dr. McCabe agreed that there is no epidemiology to either confirm or deny a causal link between an HPV vaccine and sJIA. *See generally* tr. 159-161.

Dr. McCabe disputed that the studies cited by Dr. Rose – including the Chao study, the Verstraeten study, and the Klein study – conclusively establish that Gardasil cannot play a causal role in the development of sJIA. *See* Pet. Ex. 79[33] (duplicate at Resp. Ex. H); Pet. Ex. E; [34] Pet.

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[29] Garcia-Pineras, A., et al., *Cytokine and Chemokine Profiles following Vaccination with Human Papillomavirus Type 16 L1 Virus-Like Particles*, Clin. & Vaccine Immunol., 2007; 14(8): 984-89 [hereinafter "*Garcia-Pineras*"].

[30] Evans, T.G., et al., *A Phase 1 Study of a Recombinant Viruslike Particle Vaccine Against Human Papillomavirus Type 11 in Healthy Adult Volunteers*, J. Infect. Dis., 2001; 183: 1485-93 [hereinafter "*Evans*"].

[31] Emeny, R.T., et al., *Priming of Human Papillomavirus Type 11 – Specific Humoral and Cellular Immune Responses in College-Aged Women with a Virus-Like Particle Vaccine*, J. Virol., 2002; 76(15): 7832-42 [hereinafter "*Emeny"]*.

[32] Prakken, B., et al., *Juvenile idiopathic arthritis*, Lancet, 2011; 377: 2138-49 [hereinafter "*Prakken*"].

[33] Chao, C., et al., *Surveillance of autoimmune conditions following routine use of quadrivalent human papillomavirus vaccine*, J. Intern. Med., 2011; 271: 193-203 [hereinafter "*Chao*"].

Ex. J.[35] *Chao*, which is the only epidemiological study involving Gardasil and autoimmune diseases, and which did not document any link between the vaccine and autoimmune disease, didn't specifically study sJIA. Tr. 150-51. It revealed nothing about the number of subjects who developed sJIA in the Gardasil group versus the unvaccinated control group. *Id.* Moreover, the study only included 189,000 subjects, and the incidence of sJIA is less than 1 in 100,000; as such, the study is "underpowered and is not able to be applied to an analysis of … the increased risk attributable to … developing sJIA following vaccination." Tr. 151-52.

Klein, also cited by Dr. Rose, suffers from the same deficiencies. *Id.* at 160. To enable researchers to draw any conclusions about the correlation between vaccination and sJIA, a study would have to include a million to a million and a half subjects. Tr. 152-53; Pet. Ex. 80;[36] *see also* tr. at 158 ("you are going to need to throw down on a million or 10 million subjects to … investigate the genetic susceptibility factors and immunological responses in response to whatever the putative environmental signal").

Verstraeten, which was a study of over 68,000 participants, found that the administration of Cervarix – another HPV vaccine – did not increase the participants' relative risk for contracting lupus, sJIA, systemic lupus, Sjogren's syndrome, or rheumatoid arthritis. *Verstraeten* at 1. Dr. McCabe pointed out that Cervarix includes a different adjuvant than Gardasil; that it includes immunization against only two – rather than four, as in Gardasil – HPV strains; that it is inadequately powered; and that it did not examine sJIA specifically. Tr. 362-63.

2) **sJIA is triggered by the same type of cytokine upregulation that the Gardasil vaccine is designed to produce**

sJIA is a multigenic disease that results from "an interaction between environmental and genetic factors." Tr. 118, 130. *See also* Pet. Ex. 83[37] at 1-2 (identifying, in Table 2, considerations that are relevant to an assessment of whether rheumatic disorders are due to environmental factors, and noting that there has been more progress in learning about the genetic factors that produce autoimmune diseases than there has been in learning about the environmental factors). sJIA is also autoinflammatory; it is characterized by abnormality in the functioning of the innate immune system, and it occurs in people who have a predisposed innate immune system. Tr. 118, 178-79; Pet. Ex. 46 at 1.

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[34] Verstraeten, T., et al., *Analysis of adverse events of potential autoimmune etiology in a large integrated safety database of AS04 adjuvant vaccines*, Vaccine, 2008; 26: 6630-38 [hereinafter "*Verstraeten*"].

[35] Klein, N.P., et al., *Safety of Quadrivalent Human Papillomavirus Vaccine Administered Routinely to Females*, Arch. Ped. Adolesc. Med., 2012; 166(12): 1140-48 [hereinafter "*Klein*"].

[36] Schultz, K.F., and Grimes, D.A., *Sample size calculations in randomised trials: mandatory and mystical*, Lancet, 2005; 365: 1348-53.

[37] Miller, F.W., et al., *Approaches for identifying and defining environmentally associated rheumatic disorders*, Arthritis Rheum., 2000; 43(2): 243-49.

Dr. McCabe testified that the term "idiopathic," when used in the context of sJIA, means "unique;" because it has an incidence of less than one in 100,000 people, all of whom have unique genetic and immunologic profiles, epidemiological analysis is difficult. Tr. 209-10. Therefore, the fact that there are no published case reports linking sJIA to the HPV vaccine, tr. 154, 248, is of limited relevance. *Id*. at 154.

Dr. McCabe identified the proinflammatory cytokines IL-1, IL-6, IL-18, and TNF – the upregulation of which Gardasil is designed to induce – as being involved in the development of sJIA.[38] Tr. 117, 119, 129; Pet. Ex. 17[39] at 4. Dr. McCabe agreed with Dr. Gershwin that these proinflammatory cytokines "mediate the inflammation and then the inflammation being realized by the clinical symptoms." Tr. 120; *see also Mellins* at 4. He also agreed that clinical manifestations include fever; an increase in acute phase proteins, such as C-reactive protein; increases in common myeloid progenitors; increases in platelets; increases in synovial inflammation; and increases in white blood cell recruitment and levels. Tr. 120- 21; Pet. Ex. 14 at 3 ("sJIA is characterized by prominent systemic features including high spiking fever and elevation of systemic acute phase reactants and other markers of inflammation."). "The classic disease presentation (i.e., fever, rash, joint pain)[,] together with systemic elevation of inflammatory markers[,] are indicative of an autoinflammatory disease process driven by dysregulation of the innate immune system as evidenced by a role for pro-inflammatory cytokines (e.g., IL-6, IL-1, and TNF-α) and activation of Toll-like receptor signaling pathways in the development of the disease." Pet. Ex. 14 at 3.

Although "the complexity of interactions between genetic factors and unknown environmental triggers has not been completely unraveled," "a triggering role for infections and vaccinations [in the development of sJIA] has been suggested and likely exists." Pet. Ex. 14 at 4-5; *see also* tr. 111-17; *Prakken* at 4 ("[a] genetically susceptible individual might develop a deleterious and uncontrolled response towards a self-antigen on exposure to an unknown environmental trigger …. In juvenile idiopathic arthritis, infections and vaccinations have been suggested as two candidates"). Supportive data for this conclusion comes both from human population studies that implicate infection and from "mechanistic considerations." Pet. Ex. 14 at 4. "Infections and vaccinations activate the innate and adaptive immune processes required for functional immunity, which paradoxically can result in deleterious and improperly balanced immune processes causing self tissue damage characteristic of autoimmune/ autoinflammatory disease." *Id*. The Gardasil vaccine contains a "spontaneous formation of non-infectious virus like particles [("VLPs")] that lack the HPV genome but resemble native virions;" administration of the vaccine "induce[s] high titers of neutralizing antibodies to" the L1 viral capsid proteins from four of the most common disease-associated HPV strains." *Id*. "In individuals immunized with HPV-L1 VLPs, high levels of both adaptive and innate immune cytokines are produced."

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[38] Therapeutic intervention for sJIA patients targets these cytokines. Tr. 128-129. Some of the most compelling evidence for the role of cytokines in the pathogenesis of sJIA is the successful treatment and management of the disease with therapies that inhibit TNFa, IL-6, and IL-1. Tr. 38; Pet Ex. 14 at 5.

[39] Mellins, E.D., et al., *Pathogenesis of systemic juvenile idiopathic arthritis: some answers, more questions*, Nat. Rev. Rheumatol., 2011; 7(7): 416-26 [hereinafter "*Mellins*"].

Id. Many of the cytokines elicited are the pro-inflammatory cytokines that have been implicated in the etiology of sJIA. *Id*.

According to Dr. McCabe, the fact that studies have not linked sJIA with naturally-occurring HPV infections is "irrelevant." Tr. 75-79; *see generally* Pet. Ex. 22 (discussing the efficacy of HPV vaccines in prompting an immune response).[40] The antigen dose in the HPV vaccine is much higher than it is in a natural infection; as a result, "the type of immune response, the robustness, the potency, the sustained immune response that's elicited by the vaccine, by design, is very different than what occurs in the natural infection." Tr. 77-78. There is a consensus in the scientific community that the vaccine "elicits a robust, sustained immune response that's not seen in the natural infection." Tr. 78-79. Because the natural infection does not produce the same robust, sustained immune response, it does not result in inflammation or in an upregulation of proinflammatory cytokines. Tr. 77-79.

3) The Gardasil vaccinations played a causative role in triggering Petitioner's sJIA

Dr. McCabe argued that Petitioner was genetically susceptible host for sJIA. Tr. 210. Applying the mechanisms he had identified, Dr. McCabe testified that the Gardasil vaccine "was an environmental trigger that, given her genetic and immunological susceptibility, caused her disease to manifest when it did." Tr. 154. More specifically, the vaccination "produced upregulation in [Petitioner's] adaptive and … innate immune response that included the production of proinflammatory cytokines; . . . her genetic susceptibility and immune susceptibility resulted in her presentation with symptoms that are well known and generally accepted by the scientific and medical community to be tied to inflammatory cytokines." Tr. 132; *see also* tr. 147-48 ("[Petitioner's] macrophages, which may [have] initially contain[ed] some [] control of secretion of cytokines, are being instructed, upon immunization with Gardasil, by her adaptive immune system to make proinflammatory cytokines," thereby "triggering the process."). The ongoing production of these pro-inflammatory cytokines triggered Petitioner's sJIA, which manifested clinically in November 2008. Tr. 131-32.

Dr. McCabe conceded that there is no direct evidence in Petitioner's medical record of an upregulation of cytokines after either the first or second vaccine. Tr. 182. However, Dr. McCabe observed that Petitioner's medical records contain no alternative explanation for her sJIA, either in the form of another vaccine or another infection. Tr. 195. He opined that while her immune system was capable of handling a mild infection, any infection capable of producing as robust an immune response as that elicited by the Gardasil vaccine would have had to be debilitating, and likely would have been documented. Tr. 210-11.

Dr. McCabe explained that none of Petitioner's treating physicians attributed her injury to the Gardasil vaccination because their primary goal was likely the treatment of her symptoms, not an assessment of causation, and because they lacked a way to test for upregulation of

[40] Mariani, L. and Venuti, A., *HPV vaccine: an overview of immune response, clinical protection, and new approaches for the future*, J. Transl. Med., 2010; 8; 1-8.

proinflammatory cytokines. Tr. 133, 196-97. Dr. McCabe also testified that, for the reasons set forth in subsection (b)(4), the 3.5 month interval between her first and second doses does not detract from the likelihood that the vaccine caused her sJIA, even though her vaccines were administered at different intervals than the intervals described in Pinto and other studies. Tr. 213-14.

4) **The onset of Petitioner's sJIA was temporally appropriate in light of the timing of the vaccinations.**

Dr. McCabe opined that "the expected interval between a vaccination and this autoinflammatory disease is predicted by the time period that measurable changes in the immune response are known to be elicited by the vaccine." Tr. 134-35. At least one study has shown that, among individuals who are administered a quadrivalent HPV vaccine at zero, two, and six months, over 99% of subjects experience a "robust" immune response within seven months. Pet. Ex. 26[41] at 4; tr. 19-20, 135-36.

According to Dr. McCabe, a vacinee's immune response starts to rise after administration of the first vaccine and continues to rise through the second, and possibly the third, dose of vaccine. Tr. 136-37. Dr. McCabe cited the Frazer study, which conclusively documents, among women who received three quadrivalent HPV doses, increased levels of antibody titers over a 5-year period:

[41] Joura, E.A., et al., *HPV antibody levels and clinical efficacy following administration of a prophylactic quadrivalent HPV vaccine*, Vaccine, 2008; 26: 6844-51 [hereinafter "*Joura*"].

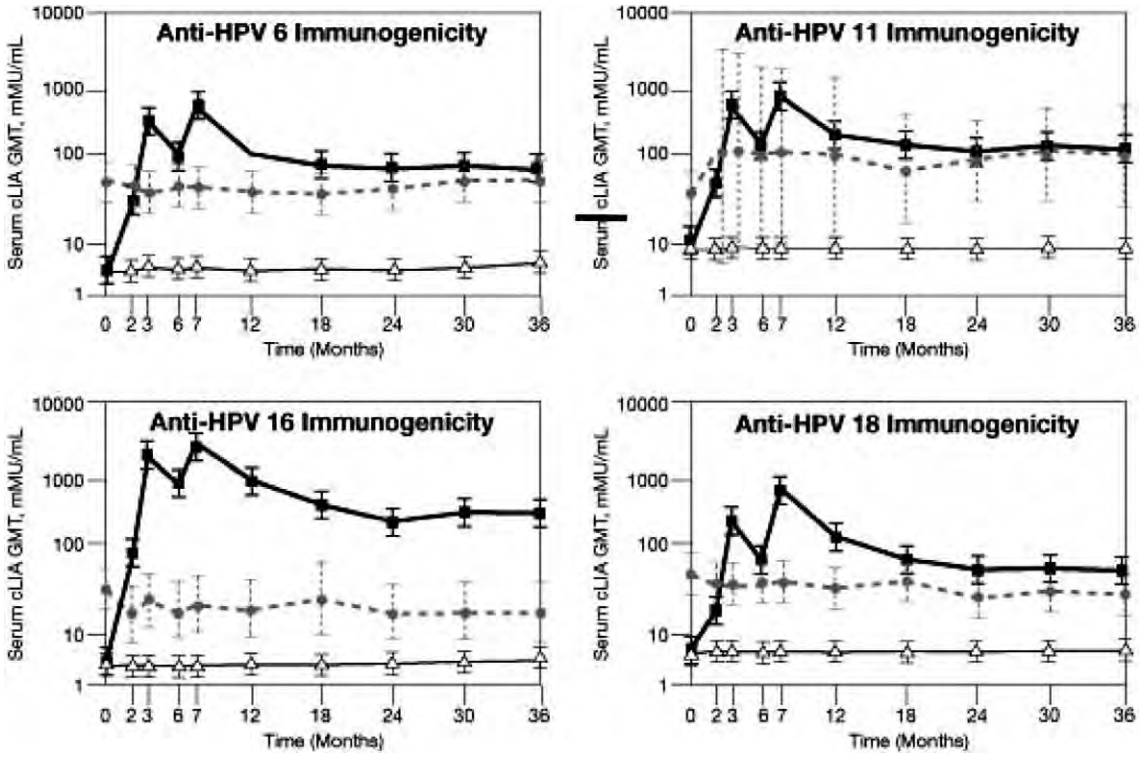

Figure 2 Immunogenicity results from a double-blind, placebo-controlled, dose-ranging study of quadrivalent HPV (types 6, 11, 16, 18) L1 VLP vaccine in 1106 young women indicated that vaccine-induced anti-HPV 6, 11, 16, and 18 geometric mean titers (GMTs) peak at month 7 and gradually decrease to reach a plateau at Month 24. The per protocol immunogenicity (PPI) cohort comprised subjects who were naïve to HPV 6, 11, 16, and 18 infection at baseline, were free of infection with the same vaccine HPV type, and who received all three vaccine doses. cLIA = competitive luminex immunoassay, GMT = geometric mean titer. •, per-protocol subjects; •, baseline HPV type seropositive and polymerase chain reaction-negative subjects (placebo group); 6, per-protocol placebo. Adapted from Villa LL et al.

Frazer at 4 (internal citations omitted); tr. 136-37. The results summarized in *Frazer* suggest that "vaccination induced a marked immune response, beginning approximately 1 month after the initial dose, peaking at approximately month 7, and thereafter declining to a stable plateau for 2.5 years after the last vaccine dose." *Frazer* at 4. Dr. McCabe's opinion, therefore, was that the timing of Petitioner's clinical presentation for sJIA – in November 2008, approximately seven months after she was administered the first dose of Gardasil – was temporally appropriate. Tr. 138-39.

Dr. McCabe disagreed with Dr. Rose that upregulation of proinflammatory cytokines occurs within 24 to 48 hours: "it takes days to mount a primary immune response, meaning an immune response where we're just looking at, focused on the proliferation of T cells." Tr. 140. Based on study data, Dr. McCabe testified that peak cytokine and antibody production occurs at approximately one month after the second vaccine dose. Tr. 191-93.

At hearing, Dr. McCabe gave two explanations for his theory that Petitioner experienced an acute innate system reaction almost five months after the administration of the second vaccine, and approximately four months after peak cytokine production. First, he explained that the second dose of the vaccination caused a more "sustained" and "robust" reaction. Tr. 184, 186 (noting that most, if not all, vaccines include a second dose as a booster to stimulate

secondary responses). Acknowledging that studies have documented a slight "downtick" in antibody levels around a month after administration of the second HPV vaccine, Dr. McCabe pointed out that the overall increase in antibody titer is so large after the first and second vaccines that these slight decreases are relatively meaningless: "there is a large – a high level of both immunoglobulin antibody and cytokine that I'd expect to be present even after the peak, even after the second [immunization]," tr. 193-94; "to perseverate on the minor changes that occur in antibody titer between month three and month seven … you're missing that much of the potency, the robustness of the response, is occurring within the time frame of those first two immunizations." Tr. 188. He cited at least one study for the proposition that "the highest increments in … cytokine responses were seen after the second immunization (i.e., at month 2)." Pet. Ex. 32 at 9;[42] tr. 93.

Second, Dr. McCabe explained that the production of cytokines was merely the initiation of Petitioner's immune response:

> it's not just the wave of cytokines … that come from immunization, but it's the regulatory response and the continued development of the immune system, both in the context of a response to the vaccine and this response that produces the disease. So, [the vaccine] starts the production of those cytokines … and it's changed her cells and it's changed her immune system and she's had … other genetic and immunological preconditions that contribute to the development of her disease at that time.

Tr. 194. As Petitioner clarified in her post-hearing brief, the analysis of temporal association involves two distinct processes: the development of sJIA and the development of immunity provided by Gardasil. Pet. Brief at 19-20; tr. 395-96.

Dr. McCabe also explained in detail why, notwithstanding the lack of a third Gardasil shot, the timing of onset of Petitioner's sJIA was plausible. Dr. McCabe testified that the first two shots provided an ongoing stimulus to Petitioner's adaptive and innate immune systems. Tr. 136-38, 185, 419-21. Any contribution of the third vaccine to the robustness of Petitioner's immune response would have been minor compared to the contributions of the first two vaccines. Tr. 189-90; *see also* tr. 139, *Pinto* (noting that, according to the Pinto article, the peak cytogram response occurs within the time frame of the second HPV immunization). Thus, even though there are no known studies documenting subjects' immune response in the absence of a third shot, the studies referenced by Dr. McCabe – which document almost-peak cytokine production approximately a month following administration of the second vaccine – are a sufficient basis, in his view, upon which to conclude that the timing of onset of Petitioner's sJIA was proximate to the administration of the first two Gardasil injections. Tr. 190-93.

Dr. McCabe did agree that in light of the timing of onset, he would have been less inclined to view the vaccine as causal if Petitioner had received only one dose of the vaccine. Tr.

[42] Pinto, L., et al., *Cellular Immune Responses to Human Papillomavirus (HPV) – 16 L1 in Healthy Volunteers Immunized with Recombinant HPV-16 L1 Virus-Like Particles*, J. Infect. Dis., 2003; 188: 327-38 [hereinafter "*Pinto 2*"].

182-83 (observing that, if Petitioner had received only one vaccination, the onset of her sJIA should have occurred in approximately two months).

ii. Respondent's Argument

1. Dr. Rose's Qualifications

Dr. Carlos Rose graduated *summa cum laude* from the University of Buenos Aires School of Medicine in 1977. Resp. Ex. B at 1. He completed his pediatric residency and pediatric rheumatology training at Thomas Jefferson University; he completed his fellowship training at the University of Pennsylvania. Tr. 222-23. Since 1994, he has been the chief of the Division of Rheumatology, in the Department of Pediatrics, at DuPont Hospital for Children in Delaware. Resp. Ex. B at 7; tr. 222. He has been a member of the American Board of Pediatrics since 1997 and of the American Board of Pediatric Rheumatology since 1998. Tr. 223; Resp. Ex. B. at 3-4.

At the time of the hearing, Dr. Rose testified that he spent approximately 30-40% of his time in clinical practice, treating clients "with mostly inflammatory conditions, including general arthritis … systemic among them, lupus, [and] typical pediatric rheumatology diseases." Tr. 223-24. He has spent a portion of his remaining time researching the mechanisms of autoinflammatory diseases and the measurement of cytokines. Tr. 225-27, 231-32. Although he had published numerous articles, none had been on the subjects of sJIA or Gardasil. Tr. 235.

At hearing, Dr. Rose was qualified as an expert in pediatric rheumatology. Tr. 236.

2. Dr. Rose's Theory

Dr. Rose agreed with Dr. McCabe that sJIA results from innate immune system dysfunction, and that it is characterized by the dysregulation of specific cytokines. Resp. Ex. A at 4 ("[B]ased on its clinical features and gene expression profile[, sJIA is] . . . one of the auto-inflammatory diseases likely associated with dis-regulation of cytokine networks likely IL-1 and IL-6 rather than the adaptive immune system") (internal citation omitted); tr. 241. Dr. Rose also agreed that sJIA is an auto-inflammatory, not an autoimmune, condition, and that it has many triggers. Tr. 241-42, 297. Dr. Rose did not agree, however, that the Gardasil vaccine played a role in the development of Petitioner's sJIA. Tr. 237. In almost 30 years of clinical practice in rheumatology, Dr. Rose has never seen a natural infection "associated with a pattern reminiscent of systemic JIA." Resp. Ex. A at 4.

Prior to the hearing, Respondent and Dr. Rose had espoused the theory that Petitioner's post-vaccine injury was, in fact, Macrophage Activation Syndrome ("MAS").[43] *See generally* Resp. Ex. A, G. Respondent ultimately conceded that Petitioner's injury was sJIA. Tr. 237. Dr. Rose, however, continued to maintain through the hearing that Petitioner's injury would be more accurately classified as MAS. Tr. 330. One reason for this theory was that Dr. Rose did not believe that Crohn's disease – with which Petitioner had been definitively diagnosed – and sJIA can co-exist. According to Dr. Rose's first expert report and his testimony at hearing, the

[43] Dr. Rose alternatively referred to MAS as "HLH." *See* tr. 347.

diagnoses of Crohn's disease and sJIA are "mutually exclusive," because sJIA is a diagnosis of exclusion. Tr. 314, 321. Dr. Rose ultimately acknowledged that studies from Western Europe document that sJIA patients "had Crohn's disease at a rate of 300-fold versus the healthy control group." Tr. 324-25. Dr. Rose explained that he had not had an opportunity to review these studies, and that he had never encountered such a case in clinical practice. Tr. 325.

Assuming that sJIA was, in fact, an accurate diagnosis, Dr. Rose's opinion was that a November 2008 viral infection – evidenced by a sore throat, fever, achiness, and irritated eyes – is the most likely cause of Petitioner's sJIA. Tr. 303, ("the preceding and most immediate viral infection could be a good alternative explanation for the triggering aspects"), 328-29.[44]

Dr. Rose also pointed out that there are no case-control prospective epidemiologic studies addressing sJIA following HPV vaccination. Resp. Ex. A at 5. Indeed, Dr. Rose cited several studies for the proposition that, statistically speaking, administration of the HPV vaccine did not increase vaccinees' risk for developing autoimmune diseases. *See generally* tr. 287-94; *Verstraeten* (finding, based on a study of over 68,000 participants, that administration of Cervarix – another HPV vaccine – did not increase the participants' relative risk for contracting lupus, sJIA, systemic lupus, Sjogren's syndrome, or rheumatoid arthritis); *Chao* (finding, based on a study of 189,000 recipients of the HPV vaccine, that the vaccine presented no increased risk for sJIA); *Klein* (finding, based on a study of the same population, that there was no increase in emergency room visits or hospitalizations, both of which one would expect to see in a patient with sJIA);[45] *Joura* (concluding that "spontaneous secretion of cytokines in the absence of any stimuli did not show any significant increases following vaccination").

Dr. Rose's position was that none of the studies cited by Dr. McCabe supports his argument that the HPV vaccine (or HPV virus-like particles) causes "the massive amount of cytokine production that you need sustained … in a person with systemic JIA day after day." Tr. 276. For the Gardasil vaccine to have caused her injury, Petitioner would have had to have "suffered an extraordinary powerful [sic] cytokine response to the vaccine (not noticed clinically … during the days immediately following the inoculation) and that the normal mechanisms of control of the cytokine response are ineffective." Resp. Ex. G at 3-4. The medical literature cited by Petitioner's experts, therefore, does not support a causative link, because it does not document a sustained pattern of cytokine upregulation in response to vaccination. *Id*. Dr. Rose argues that such a pattern is essential to show that the Gardasil can cause sJIA. *Id*.

With regard to the timing of onset of Petitioner's sJIA, Dr. Rose described as "baseless" Dr. McCabe's theory that a plausible time frame for onset should be assessed with reference to the timing of measurable changes in the immune response. Resp. Ex. G at 3. According to Dr. Rose, the body's immune response to a vaccine, as documented by sero-conversion and T cell response, has no pathological implication. *Id*. The production of pro-inflammatory cytokines

[44] Notwithstanding Dr. Rose's testimony that a viral infection was the likely cause of Petitioner's sJIA, Respondent's counsel clarified at hearing that "[w]e're not alleging an alternate cause …. there may be other explanations out there [] that may not rise to the level of . . . more probable than not." Tr. 315-17.

[45] *See also* tr. 300-02 (parenthetical).

does not always result in disease; such production is a normal, protective response that vaccines are designed to elicit, not evidence of disease onset. *Id*.

Dr. Rose testified that, if the cytokine upregulation caused by Petitioner's second Gardasil dose had, in fact, triggered her sJIA, she would have manifested the disease almost immediately. sJIA patients who take a daily dose of anakinra[46] – an IL-1 cytokine inhibitor – generally experience clinical manifestations of their disease, in the form of fever, within 12 hours of a missed dose. Tr. 307. Petitioner's medical records contain no evidence of any signs or symptoms of sJIA within the days following the first or second vaccination. *Id*.

IV. Analysis

a. Althen Prong 1.

The Supreme Court has recognized that a novel theory that is relatively unexamined by the relevant scientific community may not be as persuasive as a theory that has been thoroughly peer-reviewed. This is so because "submission to the scrutiny of the scientific community … increases the likelihood that substantive flaws in methodology will be detected." *Daubert*, 509 U.S. at 593-94 (clarifying that the lack of publication is a "relevant, though not dispositive, consideration in assessing … scientific validity"). However, special masters have also recognized that a theory's novelty is not dispositive in determining its scientific validity. *Cedillo v. HHS*, No 98-916V, 2009 WL 331968, at *111 (Fed. Cl. Spec. Mstr. Feb. 12, 2009) ("At times novel theories can be persuasive"). *See also Daubert,* 509 U.S. at 593 ("in some instances well-grounded but innovative theories will not have been published.")(internal citations omitted).

In the instant case, the undersigned finds that Drs. Gershwin and McCabe have set forth a novel, but nevertheless reliable and plausible theory by which two Gardasil vaccinations can cause sJIA. Several aspects of Petitioner's experts' theory – that Gardasil is designed to elicit proinflammatory cytokines, and that sJIA is triggered by the same type of cytokine upregulation that the Gardasil vaccine is designed to induce – are essentially uncontested by Respondent. Dr. Rose also did not dispute, as discussed by Dr. Gershwin, that sJIA is an autoinflammatory disease, and that it occurs in genetically predisposed individuals exposed to an environmental trigger. Thus, most of the mechanism of causation put forth by Petitioner's experts was not disputed. Dr. Rose did, however, disagree that the Gardasil vaccine can trigger sJIA, because he has never seen a natural HPV infection associated with sJIA, and because there is a dearth of supportive epidemiological evidence. Resp. Ex. A at 4-5; *see generally* tr. 225-300.

The undersigned finds that the lack of an association between sJIA and naturally occurring HPV infections is not dispositive. As Dr. McCabe pointed out, natural infections do not produce the same sustained immune response, or the same upregulation of proinflammatory cytokines, as does the vaccine. Tr. 77-79. This conclusion is supported by the Pinto study, which found that "[t]he cellular immune responses (lymphoproliferation and cytokine levels) after healthy individuals are immunized with []vaccine are consistently higher than those

[46] Anakinra is "a … form of the human interleukin-1 receptor antagonist, used as an antiinflammatory in the treatment of rheumatoid arthritis." *Dorland's* at 71.

previously reported in the context of natural infection. In fact, T cell responses to HPV antigens in natural HPV infection have been difficult to measure." *Pinto 2* at 10 (citations omitted).

The undersigned often relies on epidemiological evidence such as that cited by Dr. Rose in this case. However, particularly in the Prong One context, its persuasiveness is tempered by the fact that, while it may show that a vaccine has not caused a particular injury, at least to a statistically relevant extent, it cannot show that the vaccine cannot cause that particular injury. The Chao study, which followed subjects until 180 days after they had received a third quadrivalent HPV vaccine (Gardasil), did not specifically study sJIA. *See generally Chao*; tr. 150-51. Moreover, the study only included 189,000 subjects, and the incidence of sJIA in the general population is less than 1 in 100,000; as such, the study is "underpowered and is not able to be applied to an analysis of … the increased risk attributable to … developing sJIA following vaccination." Tr. 151-52. During the hearing, Dr. Rose appeared equivocal, at best, about his assertion that the studies he cited were "sufficiently powered" to be statistically useful. For example, when asked whether the Verstraeten study was sufficiently powered, Dr. Rose testified, "I did not do my power calculations. I'm sorry. That was the only thing I had at the time. I thought it was a good number. I saw they didn't see the signals. I wasn't in the peer review, I'm not an epidemiologist." Tr. 363-64. In light of the rarity with which sJIA presents, the undersigned finds that the lack of supportive epidemiological evidence is not dispositive in this case

Finally, the undersigned finds that the reliability of Dr. Rose's methodology, particularly as it relates to his definition and description of Petitioner's injury, was somewhat compromised by his insistence that Petitioner's actual injury was MAS, not sJIA, and that sJIA and Crohn's disease are mutually exclusive diagnoses.[47] *See, e.g.,* tr. 314-21. This diagnosis had no support in the medical records; almost all of the treating physicians who initially assessed Petitioner's injuries ultimately concluded that they were attributable to sJIA. Indeed, Respondent ultimately decided to concede the nature of Petitioner's injury, notwithstanding Dr. Rose's continued opinion to the contrary. Tr. 314-17, 321-23, 327-28.

Based on the foregoing analysis, the undersigned finds that Petitioner has demonstrated by a preponderance of the evidence that the Gardasil vaccine can act as a trigger and cause sJIA.

b. <u>Althen</u> Prong 2.

Petitioner was administered the first Gardasil vaccine on March 19, 2008, and the second Gardasil vaccine on June 30, 2008. Pet. Ex. 2 at 3-4; Pet. Ex. 3 at 11. Four months after the administration of the second vaccine, she presented to medical treatment providers with clinical markers of elevated proinflammatory cytokines; namely, persistent fever, myalgia, rash, and joint pain. Pet. Ex. 4 at 14; Pet. Ex. 7 at 36-38; tr. 131-32. Tests for infectious and systematic autoimmune diseases were all negative. Pet. Ex. 4 at 54; Pet. Ex. 5 at 160-68. Blood tests in

[47] The reliability of Dr. Rose's methodology was also adversely impacted by his confusion of the cytokines IL-8 and IL-18, tr. 357-358, his misreading of a chart in the Pinto article, tr. 359-360, and his reliance on statistically underpowered studies in support of his epidemiological arguments. Tr. 362-68.

December 2008 were consistent with an ongoing systemic inflammatory process. Pet. Ex. 5 at 11-16. Her ferritin, CRP, sedimentation rate, and white blood cell counts were elevated, all of which were consistent with sJIA. Tr. 13, 17, 338-44. Petitioner was successfully treated with steroids and methotrexate, both of which are drugs that inhibit the cytokines TNF-alpha, IL-6, and IL-1. Tr. 37-39; Pet. Ex. 6 at 34-36, 41.

The undersigned finds these records to be sufficient evidence of an uncontrolled activation of Petitioner's genetically susceptible innate immune system, including elevated serum levels of acute phase reactants, including C-reactive protein, as well as serum complement components, ferritin, and elevated leukocytes and platelets accompanied by a rising erythrocyte sedimentation rate, which occurred in November and December 2008. Pet. Ex. 6 at 4, 82, 86; Pet. Ex. 5 at 16, 162-65; tr. 36-37 (Dr. Gershwin opining that Petitioner's symptoms and test results in November and December 2008 were reflective of the uncontrolled activation of her innate immune system that ultimately resulted in sJIA). Although there is no direct evidence of an upregulation of Petitioner's inflammatory cytokines, the medical record contains ample circumstantial evidence in the form of her clinical symptoms, her blood test results, and her favorable response to cytokine-suppressing drugs.

Dr. Rose's argument that Petitioner's sJIA may have been triggered by a viral infection is compromised by Respondent's decision not to pursue it under an alternative causation theory. Standing alone, Dr. Rose's unembellished theory does not undermine the reliability of Petitioner's prima facie case. The undersigned finds plausible Dr. McCabe's theory that Petitioner's immune system was capable of handling a mild infection (as it had many times in the past), notwithstanding her genetic predisposition to sJIA; Petitioner's immune system was more likely to, and did, produce a "dramatic" response to the Gardasil vaccination, which is designed to produce such a response. Tr. 79-80, 210-11. Any viral infection capable of producing a comparable response would have had to be debilitating, and would likely have been specifically documented. Tr. 210-11.

Finally, the undersigned finds that the absence of a third Gardasil vaccine does not compromise Petitioner's theory under *Althen* Prong 2. Whether or not a third "booster" vaccination is administered, the first two Gardasil vaccinations are, by design, likely to prompt a robust, sustained immune response. Tr. 22-23. This immune response is near its peak after the second dose. *Frazer* at 4; tr. 188-90 (opining that any contribution of the third vaccine to the robustness of the immune response would have been minor compared to the first two vaccines; "to perseverate on the minor changes that occur in antibody titer between month three and month seven … you're missing that much of the potency, the robustness of the response, is occurring within the time frame of those first two immunizations."); *see also Pinto 2* at 6-7, which found that the further increases in cytokine levels from post-dose two to post-dose three of the vaccine "were, for the most part, small and nonsignificant."

Accordingly, the undersigned finds, by a preponderance of the evidence, that Petitioner's Gardasil vaccinations played a causative role in the development of her sJIA.

c. **Althen Prong 3**.

Both of Petitioner's experts testified that four and a half months after the second Gardasil vaccination – and seven to eight months after the first vaccination – are appropriate intervals between vaccination and onset. Tr. 16-30, 134-45. Dr. Gershwin opined that the protective response to the Gardasil vaccination takes about seven months after administration of the first shot. Tr. 18-19. Dr. McCabe cited numerous articles for his opinion that a vaccinee's peak immune response is likely to occur around seven months after the first Gardasil vaccination. Tr. 138. In light of the undersigned's finding that development of sJIA is triggered by the upregulation of the same cytokines as those peaking in response to the Gardasil vaccine, it is reasonable to conclude that the timing of onset of Petitioner's sJIA would be consistent with the peak cytokine responses documented in the studies cited by Petitioner. *See, e.g., Pinto 2* at 1 ("The strongest cytokine responses at month 7 were observed in individuals with high antibody titers at month 2, suggesting that neutralizing antibodies generated by initial vaccination may augment T cell responses to subsequent booster vaccinations."). *See generally Prakken, Pinto, Pinto 2, Garcia-Pineras, and Evans*.

Dr. Gershwin's testimony that there may be a significant period of time between the incidence of cytokine dysregulation and the "breakthrough" that leads to clinical manifestation of sJIA, tr. 26-28, 30, and that this latency period may last months, tr. 19-20, 50, was also persuasive on the temporal issue.

The undersigned finds that Dr. Rose's *Althen* Prong 3 theory – that onset should have occurred much earlier – simply lacks substantiation in the record. The undersigned acknowledges Dr. Rose's argument that sJIA patients who miss doses of their cytokine inhibitors generally experience symptoms within 12 hours. However, that timing is associated with the recurrence of sJIA, where the manifestation threshold is already met, and is therefore inapposite.

The undersigned finds that Petitioner has proven, by a preponderance of the evidence, that there is a proximate temporal relationship between Petitioner's Gardasil vaccinations and the onset of her sJIA.

V. Conclusion

For the reasons set forth above, the undersigned finds that Petitioner has shown by medical records and competent medical opinion that her medical condition was "more likely than not" vaccine-caused, and that she is entitled to compensation. This case is now ready to proceed to damages.

IT IS SO ORDERED.

s/Lisa Hamilton-Fieldman
Lisa Hamilton-Fieldman
Special Master